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Dockets Management Branch (HFA-305)
Food and Drug Administration
5630 Fishers Lane, Rm. 1061
Rockville, MD 20852

RE: Docket No. 00D-1335: Draft Guidance to Industry: Allergic Rhinitis: Clinical Development Programs for Drug Products.

Merck & Co., Inc, is a leading worldwide, human health product company. Merck's corporate strategy - to discover new medicines through breakthrough research - encourages us to spend more than $2 Billion, annually, in Research and Development (R & D). Through a combination of the best science and state-of-the-art medicine, Merck's R & D pipeline has produced many of the important pharmaceutical products on the market today.

Merck supports regulatory oversight of product development that is based on sound scientific principles and good medical judgment. Regulators must be reasonable, unbiased and efficient when they review the quality, effectiveness and safety of our products. It is in both of our interests to see that important therapeutic advances reach patients without unnecessary or unusual delays.

Merck has brought SINGULAIR to the medical community and to patients with chronic asthma for whom it provides a safe and effective treatment via a novel mechanism of action. Merck is committed to continuing to develop important new medicines for the treatment of respiratory diseases, including asthma and COPD, and for the treatment of allergic rhinitis. For these reasons, Merck is very interested in, and we feel well qualified to comment on the proposed FDA Draft Guidance for Industry for the Clinical Development Programs for Drug Products for the Treatment of Allergic Rhinitis.

Merck commends the Agency for developing this document and appreciates the opportunity to provide comments on this draft guidance.

General Comments

Meta Analysis.

The draft guidance did not address the issue of pooling of studies for an integrated summary of efficacy and safety, although it did recognize the possibility that individual trials may fail

to show effectiveness despite appropriate design and implementation (and the cause may not necessarily be directly related to the power of study).

Merck believes it is important for the Agency to recognize the utility of the use of meta-analyses (or pooled analyses) in studying the treatment effects of various agents in allergic rhinitis. A New Drug Application (NDA) presenting a positive meta-analysis with a large number of patients (with smaller confidence intervals) can provide more evidence and confidence as compared to a NDA with only two positive individual trials with a small number of patients (with larger confidence intervals).

Merck recommends that the guidance include a specific discussion of pooled analyses.

Combination Products

The document did not address trials of combination products. Because the treatment of allergic rhinitis often necessitates the use of several medications to achieve greater relief of symptoms and because, in fact, many products have been developed as fixed combination therapies, Merck recommends that the Agency address the requirements for registration of combination products in this guidance.

Specific Comments

Dose Selection; lines 65-71

Merck believes that the dose selection section as currently stated is too restrictive. Merck believes that full determination of the dose-response relationship and the identification of the lowest effective dose in allergic rhinitis may not be necessary for drugs which have a wide therapeutic margin and for which efficacy and tolerability have been demonstrated in allied diseases (e.g. asthma).

Merck recommends that this section should explicitly allow for other considerations in evaluating dose selection, in particular to include consideration of the therapeutic window and the overall risk/benefit assessment.

Specific Safety Monitoring; line 81

Merck agrees with the Agency that the determination of the safety profile of some classes of drugs should include specific evaluations because of the known potential toxicity of drugs in these classes, regardless of the disease being treated.

Consequently, Merck recommends that the Agency, in its guidance on specific class safety evaluations, place stronger emphasis on drug classes rather than on their use in allergic rhinitis. Our recommendation is that the phrase be reworded to read: "For some classes of drugs that may be used in allergic rhinitis (particularly drugs in the antihistamine class)..."

Specific Safety Monitoring; line 106

Merck believes that this paragraph presents the same issue as discussed above regarding possible class effects.

Merck recommends that the sentence be reworded to place proper emphasis on the class of drugs regardless of the disease rather than on their specific use in allergic rhinitis.

Long-Term Safety Data; lines 112-117

Merck endorses and applies the ICH guidance on extent of population exposure to provide long-term safety data for a new chemical entity. However, we believe that chronic administration of entities for up to 6 months and 1 year poses problem with respect to the design of clinical trials in patients with seasonal or perennial allergic rhinitis (SAR and PAR, respectively). The pivotal trials in SAR and PAR are of short duration (2 and 4 weeks for the double blind period, respectively) and while extension protocols may be proposed to gather additional safety data, it may be difficult to implement such long term administration and follow up in a disease which mostly is not treated chronically for one year.

Merck recommends that the Agency clarify its position on this issue and provide practical guidance for the design and implementation of chronic administration clinical trials in patients with allergic rhinitis, which would satisfy the requirement to provide long-term safety data for new drugs for the treatment of allergic rhinitis. In addition, Merck recommends that the guidance also stipulate that it may be appropriate for the safety database to account for patients from other patient populations who have been exposed to the same drug at the same or higher doses (e.g., patients with asthma).

Line 282

Merck recommends to clarify the sentence by specifying which additional safety data is required for one month for oral products. We believe that the Agency meant "...1 month of additional **specific pediatric** safety data for oral products.." as modeled after the preceding statement regarding intranasal products.

Corticosteroids issues; lines 288-314

Merck fully supports the requirement to study the hypothalamic-pituitary axis (HPA) response for intranasal corticosteroids as well as the requirement to perform a growth study in prepubertal children.

Trial Design; lines 358-362

Merck would like to suggest that, due to the clustering of sites in allergic rhinitis studies, pollen counts could be collected in the geographic regions where the study is performed instead of at each individual site. In addition, we would like to point out that pollen counts have a weak correlation with efficacy. Merck believes that additional information on exposure of patients to the relevant allergens, collecting the number of rainy days, and the extent of patient exposure to outdoor air would not necessarily be helpful and poses some practical difficulty. Indoor air is not necessarily devoid of allergens. Also, it has not been validated that measuring the extent of patient exposure to outdoor air is related to symptoms. Merck recommends that the guidance stipulate that measurement of these various parameters is clearly optional.

Trial Design; lines 364-366

Merck understands and agrees with the Agency on the principle that efforts should be made to reduce the variability in allergen exposure. However, Merck believes that the guidance may be too restrictive by providing a number of days for recruitment (albeit as an example) because of the usually large sample size and the unpredictable variability in the weather in allergic rhinitis trials.

Merck recommends that the guidance continue to reflect the principle at issue but instead of providing a rather precise number of days, stipulate that randomization should take place over the shortest time period which is logistically feasible given the size of the trial(s) and the variability in the weather.

Inclusion Criteria; lines 374-375

Merck recommends that the Agency clarifies that the requirement for a minimum documented history of SAR for 2 years before study entry is meant for adult and/or older adolescent patients as it is impossible or unlikely to require this long history in younger pediatric patients (at least in those who are <5 years).

Inclusion Criteria; lines 391-393

Because the acceleration phase of immunotherapy generally takes up to 6 months overall, Merck recommends that the period in which patients should not start immunotherapy be extended to 6 months instead of 1 month as currently stated in the draft guidance.

Exclusion Criteria; lines 408-409

In light of the efficacy of montelukast in seasonal allergic rhinitis, Merck recommends that leukotriene receptor antagonists (LTRA's) be added to the list of excluded medications.

Exclusion Criteria; lines 413-420

For the reason stated above, Merck recommends that LTRA's be added to the list of medications which need to be washed out and recommends that this period be one month.

Rating System; lines 477-504

While Merck recognizes that the 0-3 scale for symptom severity rating is commonly used, we wish to point out that there has been no published studies demonstrating its construct validity, responsiveness, or reproducibility and that, in the future, other measurement tools may be developed which may be able to detect treatment differences with more precision and accuracy. Therefore, Merck recommends that the guidance avoid using this specific scale example with the appearance of endorsement.

Instantaneous Symptom Score; lines 480 and 506-514

Merck believes that the instantaneous symptom score may not be the only means of demonstrating effectiveness at the end-of-dosing interval. Merck recommends that the guidance allow for other means to demonstrate end-of-dosing interval efficacy/activity, including other pharmacodynamic activity endpoints (e.g., nasal airway resistance). In addition, Merck recommends that the guidance indicate that instantaneous symptoms scores can also be used to evaluate onset of action instead of only end-of-dosing interval effects.

Collection of Data; lines 557-558

Merck recommends to replace 'symptoms' with 'measures' and 'all' with 'other' as other measures can be collected in addition to symptoms, e.g., Quality of Life.

Time to Maximal Effect; lines 560-566

Merck believes that the definition used for time to maximal effect fails to recognize the random fluctuation of symptoms over time. Merck recommends that the guidance encourage sponsors to study and evaluate time response profile using appropriate methods (e.g., repeated measures or response modeling).

Duration of Effect (End-of-Dosing Interval Analysis); lines 568-574

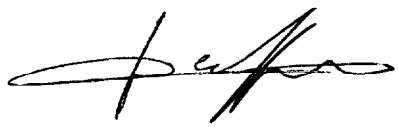
Please see previous comments on assessment of end-of-dosing interval efficacy.

SAR Prophylaxis Trials; lines 630-632

Merck recommends the Agency elaborate on the endpoints to be proposed in a SAR prophylaxis trial.

Merck welcomes the opportunity to provide comments on this draft guidance which, from our perspective, will clarify some of the outstanding issues. We trust that these comments will be considered in further development of the proposed guidance.

Sincerely,



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